DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Office of Policy, Planning, and Legislation HF-11
5600 Fishers Lane
Rockville, MD 20857

MAY 7 2002

Donna L. Bade
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200 West Madison Street, Suite 2670
Chicago, IL 60606

Re: Docket No. 98N-0583/PSA

Dear Ms. Bade,

In your recent petition for stay of action, dated March 12, 2002, regarding the final export notification and recordkeeping rule (66 Fed. Reg. 65429 (December 19, 2001)), you raised several questions regarding interpretations of the statutory export requirements or the final rule.

On March 18, 2002, we notified you that the agency intended to grant a 90-day stay of the rule's effective date. We now take this opportunity to respond to the questions and other issues raised in your petition.

As a preliminary matter, we note that, as part of your justification for a stay, your petition indicated that executing a certification that an export does not conflict with a foreign country's laws would not be a simple process and would require lengthy legal research and evaluation of foreign import laws to ensure that the certification is accurate. However, the statutory requirement at issue, section 801(e)(1)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) has remained essentially unchanged since 1938.[1] We believe that a prudent company would have, even in the absence of the final rule, taken steps to ensure that the product intended for export "is not in conflict with the laws of the country to which it is intended for export" as required by section 801(e)(1) of the Act. Given the provision's 64-year existence, lengthy legal research and evaluation of foreign import laws should not suddenly have become necessary as a result of the final rule.

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We also note that your petition indicated that "additional wording on the label for

[1] See Public Law 75-717. In 1938, the provision was codified at 21 U.S.C. 381(d). Congress renumbered the provision as 21 U.S.C. 381(e)(1) as a result of the Drug Export Amendments Act of 1986 (Public Law 99-960).

compliance with section 801(f) of the FDA Export Reform and Enhancement Act . . . may not be viable or may make a drug appear unsafe" (Petition for Stay at page 3). However, the final export notification and recordkeeping rule does not involve or affect labeling issues under section 801(f) of the Act. But persons exporting a drug under section 801(f) of the Act must also comply with section 801(e)(1) of the Act and keep records to show compliance with section 801(e)(1) of the Act.

Your petition also stated that "there are many gray areas where the scope of the regulations is unclear" and sought clarification of the final rule's applicability to various products and components (Petition for Stay at pages 3-4).

The final rule did not attempt to describe the types of products that are subject to the statutory export requirements because the Act itself describes which products fall within sections 802 and 801(e)(1) of the Act. For example, section 802(a) of the Act clearly states that:

> (a) A drug or device–
> (1) which, in the case of a drug–
> (A)(i) requires approval by the Secretary under section 505 before such drug may be introduced or delivered for introduction into interstate commerce; or
> (ii) requires licensing by the Secretary under section 351 of the Public Health Service Act or by the Secretary of Agriculture under the Act of March 4, 1913 (known as the Virus-Serum Toxin Act) before it may be introduced or delivered for introduction into interstate commerce;
> (B) does not have such approval or license; and
> (C) is not exempt from such sections of Act; and
> (2) which, in the case of a device–
> (A) does not comply with an applicable requirement under section 514 or 515;
> (B) under section 520(g) is exempt form either such section; or
> (C) is a banned device under section 516, is adulterated, misbranded, and in violation of such sections or Act unless the export of the drug or device is, except at provided in subsection (f), authorized under subsection (b), (c), (d), or (e) or section 801(e)(2). . . .

Thus, section 802 of the Act applies to exports of *unapproved* drugs and devices. It does *not* establish requirements for exports of approved drugs or devices. If a drug or device has marketing approval in the United States and otherwise complies with all applicable requirements under the Act, the product may be introduced or delivered for introduction into interstate commerce, including exportation (see, e.g., sections 201(b), 301(d), 505(a), and 515(a) of the Act). Therefore, to the extent that your petition's reference to "marketed products" (Petition for Stay at page 3) was meant to be synonymous with approved drugs and devices, the export

requirements at section 802 of the Act and the final rule do *not* apply.[2]

As for section 801(e)(1) of the Act, as we stated earlier, the statutory requirements have remained essentially unchanged since 1938. Section 801(e)(1) of the Act applies to the export of food, drugs, devices, and cosmetics that would otherwise be considered to be "adulterated or misbranded under this Act." Section 201(f) of the Act defines "food," section 201(g) of the Act defines "drug," section 201(h) of the Act defines "device," and section 201(i) of the Act defines "cosmetic." The statutory definitions at section 201 of the Act apply to section 801(e)(1) of the Act. Accordingly, as in the case of section 802 of the Act, a food, drug, device, or cosmetic that is legally commercially marketed in the United States is not subject to the export requirements at section 801(e)(1) of the Act.[3]

Your petition sought clarification as to the final rule's applicability to specific products and components. The final rule implements the export notification and recordkeeping requirements contained in section 802 of the Act, and also describes the types of records that would be satisfactory to show compliance with the export requirements in section 801(e)(1) of the Act. Sections 802 and 801(e)(1) of the Act provide exemptions to otherwise applicable provisions of the Act. If the product is not subject to the Act, sections 802 and 801(e)(1) of the Act do not apply. But if the product is subject to the Act and does not comply with the relevant requirements of the Act for commercial distribution and sale in the United States, it may not be exported unless it meets the requirements of section 802 or 801(e)(1) of the Act, as applicable. Accordingly, whether an exported product is subject to section 802 or 801(e)(1) of the Act turns on the status of the product under the Act. For example, if the product is an unapproved new drug subject to section 505 of the Act, it must comply with section 802 of the Act if it is to be exported.

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[2] As for "marketable products," we do not know whether you mean products that deviate from the FDA-approved product in some fashion, products that could be marketed in the United States if the manufacturer took the necessary steps to obtain marketing approval, or products that are approved in the United States but might not be sold domestically. In general, if a product deviates from the approved product in some manner, such as a drug with a different indication for use or different ingredient, the product would be a "new" product and require its own approval. If a manufacturer could obtain FDA approval for a product, but has declined or failed to obtain such approval, the product is still unapproved. However, if a product has FDA approval, it remains "approved" even if the sponsor elects to discontinue sales in the United States.

[3] As in footnote 1 regarding "marketable products," we are unsure as to your interpretation of "marketable products." In any event, if the product to be exported is adulterated or misbranded, then a person wishing to export that product would have to comply with section 801(e)(1) of the Act.

The responses below to your listed examples are based on the limited information in your petition, and are intended to provide general information as to how products might be subject to section 802 or 801(e)(1) of the Act. The facts of a particular product may result in a different application of these provisions. We are unable to provide clarification for some of your examples because we do not know whether those examples encompass finished products.

- Research and development materials. This is a broad term, and we cannot determine whether the materials you describe are finished products that are to be used in laboratory tests, finished products to be used in clinical trials, components to be used in calibrating machinery, or some other category. For example, if these materials include investigational new drugs for clinical trials, then the export could be subject to section 802(b)(1) or (c) of the Act, depending on whether the drug has received marketing authorization in a so-called "listed country," or is intended for investigational use in a listed country.

- Samples. If "samples" means samples of a finished product and that product is not approved for use or legally marketed in the United States, then sections 801(e)(1) and 802 of the Act could apply. The export provisions do not make distinctions for "free" samples, or for samples attached to another product. As a result, a "free" sample of an unapproved drug attached to another product must comply with section 802 of the Act if it is to be exported. Likewise, the product to which the sample is attached must also comply with the export requirements applicable to that non-sample product, if the product is subject to the Act and is adulterated, misbranded, or unapproved. Section 503 of the Act provides additional requirements for drug samples that may be applicable.

- Bulk products. As in the example of research and development materials, we cannot determine whether the materials you describe include finished products that are to be shipped in bulk or components, such as active ingredients, that are to be shipped in bulk. For example, a finished drug that does not have FDA approval and is intended for export would be subject to section 802 of the Act, but a shipment of bulk inactive ingredients would not be subject to section 802 of the Act because such bulk inactive ingredients do not require approval under section 505 of the Act and, therefore, do not fall within the scope criteria at section 802(a)(1)(A) of the Act. Such exports, however, must comply with section 801(e)(1) of the Act if the products are adulterated or misbranded.

- "Intermediaries" (which we interpret as being intermediate products), subassemblies, and raw materials. Such products are probably not within the scope of section 802(a)(1) of the Act because these items, in general, do not require FDA approval or do not need to comply with premarket approval

requirements.[4] Whether such products are subject to section 801(e)(1) of the Act may depend on whether they would otherwise be considered to be "adulterated or misbranded under this Act." For example, even though a empty gelatin capsule might be a "drug" under section 201(g) of the Act (by virtue of being a component of a drug), the empty gelatin capsule might fall outside section 801(e)(1) of the Act if it would not be considered to be adulterated or misbranded under the Act.

- IND or IDE products. If the IND or IDE covers the foreign clinical trial, exports to that trial are not subject to sections 801(e)(1) or 802 of the Act. In general, an IND or IDE represents an exception to the statutory requirement that requires a drug or device to have an approved application in order to move in interstate commerce. Because section 201(b) of the Act defines "interstate commerce" in a manner that includes exportation, a person who has a valid IND or IDE for a foreign clinical trial may export the investigational new drug or device to that trial without having to comply with sections 801(e)(1) or 802 of the Act.

- Toothbrushes with dentifrice. Such products would be subject to both sections 801(e)(1) and 802 of the Act, if the dentifrice is a regulated as a drug and is an unapproved new drug, rather than a cosmetic, or if the toothbrush is device to which the provisions of section 801(e)(2) of the Act apply. But if, for example, the dentifrice is regulated as a cosmetic and the toothbrush is misbranded, the export would be subject to section 801(e)(1) of the Act alone.

- Menstrual pads with antiperspirant. Such products would probably be subject to section 801(e)(1) of the Act if the product would otherwise be considered to be adulterated or misbranded if sold or offered for sale in the United States. The menstrual pad would be a "device," and the antiperspirant would probably be a "cosmetic" under the Act.

With respect to combination or "mixed" products – i.e., products that constitute a combination of two or more different FDA-regulated products – we must disagree with the suggestion that the final rule is ambiguous. There have been numerous opportunities since the enactment of the FDA Export Reform and Enhancement Act in 1996 to submit comment seeking clarification of how section 801(e)(1) and 802 of the Act apply to combination products. The

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[4] Your petition stated that exportation of silica intended for use in a toothpaste might be subject to section 802 of the Act because drug components are, themselves, "drugs" under section 201(g) of the Act. Bulk silica, if it is a raw material, would not generally be subject to the approval requirements under section 505 of the Act. However, silica intended for use in fluoride toothpaste would be a drug and would be subject to the export requirements in section 801(e)(1) of the Act if the silica were adulterated or misbranded.

agency did not receive comments following the enactment of the 1996 Export Act's enactment, or in response to the draft guidance document in 1998 (see 63 Fed. Reg. 32219 (June 12, 1998)), or the proposed export notification and recordkeeping rule in 1999 (see 64 Fed. Reg. 15944 (April 2, 1999)) that asked the agency to address combination products. Moreover, the statute adequately defines which products are subject to sections 801(e)(1) and 802 of the Act.

Nevertheless, we note that the agency has provided guidance to the public regarding certain issues of primary center jurisdiction regarding combination products. For example, intercenter agreements exist to describe the allocation of administrative responsibility for categories of products or specific products (see, e.g., 21 CFR 3.5).[5] We also note that the preamble to the final rule indicated that we would determine the applicability of sections 801(e)(1) or 802 of the Act to a product according to the product's classification or type in the United States (see 66 Fed. Reg. at 65433 (comment 12)). While the regulation of combination products does present some complex issues, those complexities are not attributable to the final rule.

Furthermore, with respect to most exports of combination products, the issue of which center has primary jurisdiction issue may be largely irrelevant. For example, if a person sought to export a drug/device combination product, and both components were unapproved, the drug would be subject to the export requirements at section 802 of the Act,[6] whereas the device could be exported under section 801(e)(2) or 802 of the Act. If the export complied with section 802 of the Act, the product could be exported. As a further example, if a person sought to export a product consisting of a combination of an unapproved drug and misbranded device, the drug would be subject to the export requirements at section 802 of the Act and the device could be exported if it complied with section 801(e)(1) of the Act. Again, if the export complied with section 802 of the Act, the product could be exported because exports under section 802 of the Act must also comply with section 801(e)(1) of the Act.

Although the export of a combination or "mixed" product may present questions as to which FDA component should receive the required notification, several options exist. For example, in the case of a combination product consisting of two components in which both components could, if they were exported individually, be exported under section 802 of the Act, the exporter could contact FDA to determine which center should be sent the notification.

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[5] While this regulation is part of a "product jurisdiction" program for FDA review of premarket applications, the principles expressed in the intercenter agreements are equally applicable to a determination as to the center with lead administrative responsibility for a combination product intended for export.

[6] Most drugs subject to the Act's export requirements would be exported under section 802 of the Act because at least one court has held that section 801(e)(1) of the Act does not apply to exports of "new drugs" (see 63 Fed. Reg. 32219, at 32221, col. 1).

Alternatively, the exporter could decide to submit notifications to both centers, even though the final rule would not require such a result. Consistent with the rule, the exporter could also could send the notification to one center, and that center could pass the notification to another center if appropriate. Moreover, this notification issue only exists if the "mixed" product consists of a drug, device and/or biologic combination, and both components are subject to section 802(b)(1) of the Act and section 802's notification requirement. If the exported product is a drug-cosmetic combination product, for example, and the product is being exported under section 802(b)(1) of the Act, the notification would go to the Center for Drug Evaluation and Research (CDER). Section 801(e)(1) of the Act does not require a notification for cosmetic exports.

Finally, your petition inquired about the proper timing of the notification required for certain exports under section 802(g) of the Act. The statute requires the notification to be provided to the agency "when the exporter first begins to export" the drug or device, and does not proscribe an exact timeframe for doing so. Companies generally provide notification contemporaneously with the first export, or soon thereafter. We not aware of any instances in which exporters have found the 1996 statutory language regarding the timing of notifications to be problematic.

Should you have any additional questions, please feel free to contact us.

Sincerely,

Margaret M. Dotzel
Associate Commissioner for Policy